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Conversion of C57Bl/6 mice from a tumor promotion-resistant to a -sensitive phenotype by enhanced ornithine decarboxylase expression.

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A transgenic mouse model was developed in which ornithine decarboxylase (ODC) can be overexpressed in a tissue-specific and regulated manner. Hair follicle keratinocytes were targeted by use of a bovine keratin 6 (K6) promoter/regulatory region, and regulation was accomplished by using the tetracycline-regulated transactivator/tetracycline-response element system. Double-transgenic mice carrying both transgenes (K6/tetracycline-regulatable transactivator protein (tTA) and tetracycline-response element/Odc) on a C57Bl/6 background had no obvious phenotypic abnormalities in the absence (Odc transgene-expressed) of doxycycline (a tetracycline analog) in the drinking water. However, induction of K6-driven tTA expression by the tumor promoter (12-O-tetradecanoylphorbol-13-acetate) (TPA) led to very high levels of epidermal ODC activity and robust hyperplasia, especially involving hair follicles. Both effects were abolished by inclusion of doxycycline in the drinking water to repress transgene expression. Finally, the number of papillomas that developed in a standard (7,12-dimethybenz[a]anthracene) (DMBA)/TPA protocol was greatly reduced in mice in which transgenic Odc expression was repressed by doxycycline. Our results demonstrated that the higher levels of ODC expression produced in the transgenic model in the induced versus the repressed condition make the normally promotion-resistant C57Bl/6 strain much more sensitive to the short-term and long-term (i.e., tumor-promoting)

effects of TPA.

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